CLINICAL PRACTICE

Infertility Evaluation and Treatment

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A couple presents after 1 year without conception despite having had sexual intercourse 2 or 3 times per week. The 36-year-old female partner has menses (lasting 3 to 5 days) every 26 to 30 days. Neither partner has active medical problems; both are taking vitamins aimed at supporting fertility. They would like to have three children. How would you evaluate and treat this couple?

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CME

THE CLINICAL PROBLEM

Primary infertility is defined as a history of no previous conception, and secondary infertility is an inability to conceive after any previously documented pregnancy. As defined by the American Society for Reproductive Medicine (ASRM), any need for reproductive technology in order to conceive is meant to be inclusive of same-sex couples, single parents by choice, persons who want to freeze oocytes, and transgender persons.[1]

Assisted conception accounts for 5% of U.S. births.[2] Although in vitro fertilization (IVF) was invented to circumvent blockage of the fallopian tubes, the expected live birth rate with IVF per round of treatment exceeds that of a couple with normal fertility in any given cycle and surpasses all other treatments to obtain a live birth (Table 1). This degree of efficacy has led to the use of IVF for the treatment of infertility due to almost any cause. However, fertility treatment is expensive in the United States, and insurance coverage is inconsistent, factors that lead to inequitable access. Only 21 states mandate partial or complete insurance coverage. Regardless of access, Black, Hispanic, and Asian persons have lower live birth rates than White persons with most treatments, particularly IVF.[3]

STRATEGIES AND EVIDENCE

HISTORY AND EXAMINATION

A comprehensive evaluation includes a detailed menstrual history and assessment of risks for anatomical infertility, such as previous pelvic surgery or infection. Medications that are potentially hazardous for pregnancy or conception (e.g., retinoids, methotrexate, and lithium) should be reviewed for replacement with appropriate alternatives. A history of testicular injury or undescended testes should be obtained, along with an assessment for androgenic steroid use, which is increasingly common among U.S. men 18 to 45 years of age.[4] An evaluation should focus on clinical information relevant to common causes of infertility: extremes of weight, signs and symptoms of polycystic ovary syndrome (PCOS; e.g., hirsutism, acanthosis nigricans, and oligomenorrhea), premature ovarian insufficiency (e.g., night sweats), hyperprolactinemia (e.g., galactorrhea), and other possible endocrine

KEY POINTS

INFERTILITY EVALUATION AND TREATMENT

- The age of the childbearing female partner is the most important predictor of live birth with natural conception as well as with assisted conception.
- The probability of live birth with a single cycle of in vitro fertilization therapy exceeds the monthly fecundability of natural conception, thereby leading to its dominant role in fertility treatment.
- At least one third of infertility cases are due to male reproductive issues that could be effectively managed with assisted conception.
- An evaluation should focus on clinical information relevant to common causes of infertility: extremes of weight, signs and symptoms of polycystic ovary syndrome, and other possible endocrine disturbances.

disturbances (e.g., hypothyroidism, type 2 diabetes, and hypogonadism). A single abnormality, if found, should not be assumed to wholly explain a couple's infertility. Complete testing of both partners is recommended in most cases. Patients' intentions with regard to their hoped-for family size and potential consideration of donor gametes or embryos can inform longer-term therapeutic options.

RECOMMENDED ROUTINE TESTING

Semen Analysis

Semen analysis is recommended and should be repeated if the results of the first analysis are outside the normal range.[5] An abnormal semen characteristic (e.g., low sperm concentration, sperm dysmotility, or abnormal morphologic features) is detected in approximately one third of couples with infertility (Table 1). In cases of a varicocele, fertilization failure, poor embryo development after IVF, or recurrent pregnancy loss, an assessment of sperm DNA fragmentation may inform a recommendation for the use of donor gametes.[6]

Ovarian-Reserve Testing

The age of the childbearing female partner is the most important predictor of live birth, regardless of ovarian reserve.[7] However, evaluation of ovarian reserve should be undertaken regardless of age. A combination of ultrasonography and serum markers assess both visible and implied numbers of ovarian follicles as well as the likely response to gonadotropins. The number of all follicles 2 mm to 10 mm in diameter (measured with the use of ultrasonography) in both ovaries determines the antral follicle count.[8] Antimüllerian hormone, which is not dependent on the stage of the menstrual cycle, is produced by the granulosa cells of early-developing follicles and is the most direct serum biomarker that quantifies the relative pool of primordial ovarian follicles.[9] Measurement of the levels of follicle-stimulating hormone (FSH) and estradiol in the early follicular phase (menstrual cycle days 2 to 4, when FSH is typically at its follicular-phase peak) provides indirect information about ovarian reserve. Because more FSH is required to cause follicular maturity as ovarian reserves dwindle, the follicular phase shortens with earlier elevation of estradiol. Therefore, elevated levels of FSH and estradiol indicate decreased ovarian reserve. Adequate ovarian reserve thresholds are shown by an antral follicle count of at least 12, a level of antimüllerian hormone greater than 1 ng per milliliter, an FSH level of less than 10 IU per liter, and an estradiol level of less than 80 pg per milliliter. Decreased ovarian reserve is observed in approximately 26% of patients presenting to IVF centers in the United States.[10] Patients with decreased ovarian reserve are usually directed toward more aggressive treatment because the course of progression to ovarian failure in such patients is unpredictable and may be rapid. Very high levels of antimüllerian hormone (greater than approximately 6 ng per milliliter[11]) or antral follicle counts (greater than 25[12]) indicate the presence of PCOS and predict a strong response to ovarian stimulation.

Ovulatory Evaluation

Release of a viable egg is mandatory for conception. Women reporting monthly menses every 28 days are presumed to be ovulatory, and routine confirmation of ovulation is not necessary.[13] Premenstrual symptoms such as breast tenderness and abdominal bloating are supportive of ovulation. Home urine testing for the midcycle luteinizing hormone (LH) surge is widely available, and a positive surge result approximately 14 days

Table 1. Infertility Causes, Prevalence, and Management Approaches.*

Cause	Prevalence	Treatment Option (Reported Outcome per Treatment Cycle)
	%	
Ovulatory dysfunction	25[15]†	Induction of ovulation (live birth, 35.4%)[38]
Polycystic ovarian syndrome	8–13[19]‡	Letrozole[21] (live birth, cumulative for up to five cycles, 27.5%) Clomiphene (live birth, cumulative for up to five cycles, 19.1%)
Functional hypothalamic amenorrhea	1[25]‡	Cognitive behavioral therapy[24] (NA) Clomiphene (NA)§ Gonadotropin (NA)
Premature ovarian insufficiency	1[26]‡	Oocyte donation (live birth, 39.0%)[38]
Diminished ovarian reserve[10]	19–26[10]†	IVF (live birth, 19.9%)[38]
Uterine factor	2–17[33]†	Individualized (NA)
Fallopian tube patency[30]¶	11–67[46]†	IVF (live birth, 38.1%)[30,38] Hydrosalpinx removal[30] (odds ratio for clinical pregnancy, 4.66; 95% CI, 2.47 to 10.01)
Endometriosis	25–50[34]‖	IVF (live birth, 39.5%)[38]
Abnormal semen characteristics	5–40[15]	IUI (NA) IVF (live birth, 40.8%)[38]
Unexplained infertility**	15	IUI with clomiphene[36] (live birth, 23.3%) IUI with letrozole[36] (live birth, 18.7%) IUI with gonadotropin[36] (live birth, cumulative for up to four cycles, 32.2%) IVF (live birth, 39.9%)[38]

* Live birth rate is reported by the Society for Assisted Reproductive Technology as live births per initiated stimulation cycle in women younger than 35 years of age or for all donor oocyte cycles initiated.[38] IUI denotes intrauterine insemination, IVF in vitro fertilization, and NA insufficient data to report outcomes.
† Shown is the prevalence among couples with infertility.
‡ Shown is the population prevalence of the disorder.
§ Clomiphene may be considered for treatment in women with functional hypothalamic amenorrhea if the patient's initial estradiol level does not indicate complete suppression of the hypothalamic pituitary axis.
¶ Prevalence varies widely depending on the population.
‖ The prevalence of endometriosis among adults in the U.S. population is 10 to 15%.[34]
** Multiple gestation occurred in 13% of gestations with letrozole, 9% with clomiphene, and 32% with gonadotropin. There were 10 triplet gestations, all in patients who were treated with gonadotropin.

before menses is confirmatory, as is a midluteal (7 days before expected menses) serum progesterone level of 3 ng per milliliter or higher.[14] Absence of menses, infrequent menses, or inadequate progesterone production indicate oligo-ovulation or anovulation. Testing for hyperprolactinemia, PCOS (levels of androgens and 17-hydroxyprogesterone and the LH:FSH ratio), congenital adrenal hyperplasia (level of 17 hydroxyprogesterone), hypogonadotropic amenorrhea (levels of LH, FSH, and estradiol), or premature ovarian insufficiency (levels of FSH and estradiol) are indicated depending on the clinical presentation. Further testing specific to each condition may also be indicated (e.g., metabolic assessment for women with PCOS, psychosocial assessment for women with hypothalamic amenorrhea, and genetic and autoimmune workups for women with premature ovarian insufficiency).

Evaluation of the Fallopian Tubes and Uterus

Anatomical abnormalities (e.g., fallopian tube occlusion, pelvic adhesions, and other tubal abnormalities) accounted for up to 34% of infertility factors in women in one large World Health Organization study of 8500 couples with infertility.[15] Hysterosalpingography and sonohysterography with or without a saline-air device are noninvasive techniques that have largely supplanted laparoscopy to determine tubal patency as well as intrauterine

fibroids, polyps, and adhesions.[16] Both methods involve retrograde instillation of either radiologic contrast (hysterosalpingography) or saline and air (ultrasonography-based methods) to separate the uterine walls and push fluid through the fallopian tubes, which allows visualization of the uterine cavity and tubal patency.

TREATMENT

TREATMENT OF INFERTILITY ATTRIBUTABLE TO THE MALE PARTNER

A variety of products (devices and supplements) have been suggested to improve semen quality; however, none, including vitamins, have sufficient evidence to warrant their use.[17] With regard to varicoceles, no clinical trial evidence has shown that surgical treatment improves fertility.

Most treatments of male infertility involve the mechanical manipulation of semen by means of suspending a sperm concentrate in culture medium and injecting it into the uterine fundus at the time of ovulation (intrauterine insemination [IUI]), placing sperm directly onto oocytes in vitro, or mobilizing a single sperm cell and injecting it directly into an oocyte during IVF (intracytoplasmic sperm injection).

Couples in which the male partner has abnormally low motile sperm counts are candidates for IUI. For motile sperm counts below the range of 1 million to 5 million, IVF with direct sperm injection is the treatment of choice. Despite increased use of this technique to ensure against fertilization failure, a cohort study of more than 300,000 IVF cycles showed lower rates of implantation and live birth when intracytoplasmic sperm injection was performed for indications other than severe male infertility.[18]

TREATMENT OF OVULATORY DISORDERS

Although IVF is the most successful treatment option for almost all ovulatory disorders, whether to try ovulation induction or stimulation strategies first merits consideration because of the associated cost and invasiveness of IVF (Table 1). PCOS, the most common endocrinopathy in women, affects 6 to 13% of women of reproductive age worldwide.[19] A secondary analysis of randomized trials involving women with PCOS and obesity showed that deferred ovulation induction preceded by lifestyle interventions and hormonal contraception resulted in significantly more ovulation than immediate ovulation induction (with 62% vs. 45% of treatment cycles leading to ovulation).[20] Letrozole was more effective than clomiphene for ovulation induction and live birth in women with PCOS (Table 1).[21] Although helpful for preventing type 2 diabetes, metformin led to fewer 6-month cumulative live births (in 7.2% of the women who received it) than clomiphene (in 22.7%) in a large, U.S. network-based clinical trial.[22] IVF is a favorable second-line option for women with PCOS, because their increased number of ovarian follicles usually leads to highly productive egg harvesting. A Cochrane Review of 13 randomized clinical trials involving 1132 persons did not show a benefit in live births with concurrent metformin treatment during an IVF cycle.[23]

Other common ovulatory disorders that cause amenorrhea include functional hypothalamic amenorrhea (in 1% of women with amenorrhea[24,25]), premature ovarian insufficiency (in 1%[26]), and prolactinoma (in 0.3%[27]). Management of hypothalamic amenorrhea includes cognitive behavioral therapy to help address causal stressors such as low body weight or low body fat, psychogenic stress, negative energy balance, and excess exercise. Gonadotropin injections can also be used to induce ovulation. Pregnancy rates approach normal ranges when ovulatory function is reestablished.[24] Premature ovarian insufficiency is not reversible; when prolonged amenorrhea is observed, pregnancy is unlikely, regardless of treatment. Prolactinomas in women are usually responsive to medical management with dopamine agonists (cabergoline or bromocriptine); live birth rates as high as 94% have been reported once prolactin levels normalize.[28]

TREATMENT OF TUBAL AND UTERINE FACTORS

Women with fallopian tube occlusion or removal need IVF therapy to conceive. If a hydrosalpinx is present, removal or complete occlusion of the affected tube, treatment with antibiotic agents, or aspiration is recommended. Findings from retrospective studies and limited data from randomized clinical trials support this practice. In one study involving 192 women, live births occurred in 28.6% of the women who were randomly assigned to undergo hydrosalpinx removal, as compared with 16.3% (P=0.045) of the women who received no intervention.[29] A Cochrane Review reported data from five clinical trials involving

626 women that supported the benefit of hydrosalpinx removal on pregnancy rates, but the report noted that the trials produced limited data with regard to live births and the value of drainage or occlusion.[30] Given the effectiveness of IVF in producing live births, the need for hydrosalpinx removal has been questioned.

Among uterine disorders, septa (estimated prevalence, 0.2 to 2.3%) are often found during the fertility workup. Septum excision has been recommended in patients with a history of pregnancy loss, in the belief that the relatively avascular septum surface constitutes a poor implantation site. However, a randomized, international, multicenter clinical trial that compared septum removal with expectant management in women with previous pregnancy loss showed no benefit with septum resection.[31] Other uterine causes of infertility, such as fibroids and synechiae, are managed on the basis of the signs and symptoms specific to the patient. Surgical management of asymptomatic fibroids remains controversial, and treatment is currently individualized.[32] Uterine lesions are typically treated with outpatient hysteroscopic resection.[33]

TREATMENT OF ENDOMETRIOSIS

Although the estimated prevalence of endometriosis is 2 to 10% among all women, it is found in 25 to 50% of women with infertility.[34] When endometriosis is diagnosed, surgical excision or fulguration, followed by expectant management, is preferred.[35] However, since routine laparoscopy is no longer part of the infertility workup, occult endometriosis may be present. Because of the invasive and inflammatory nature of ovarian endometriosis, this disorder can reduce ovarian reserve and cause pelvic adhesions and tubal occlusions that further compromise fertility. IVF is often the preferred treatment to hasten time to pregnancy in women with severe endometriosis. However, in mild disease in which cytoreductive surgery has been performed and symptoms have not recurred, management is more consistent with that of unexplained infertility.[35]

TREATMENT OF UNEXPLAINED INFERTILITY

By definition, unexplained infertility is present when a complete workup fails to yield a cause. A stepwise approach to treatment, beginning with mild ovarian stimulation combined with IUI, is typically performed for up to 4 to 6 cycles. Clomiphene is the treatment of choice on the basis of a multicenter clinical trial evaluating the use of clomiphene, letrozole, or gonadotropins along with IUI in 900 couples with unexplained infertility (Table 1). The higher live birth rate with gonadotropin–IUI treatment in this trial was offset by its unacceptably high incidence of multiple pregnancy (32% of pregnancies) as compared with clomiphene (13%) and letrozole (9%).[36] A separate randomized trial evaluating time to pregnancy and overall cost found no benefit of performing gonadotropin–IUI before IVF if a trial of clomiphene did not result in a live birth.[37]

IN VITRO FERTILIZATION

In 1978, the year of the first live birth of a baby conceived through the use of IVF, the probability of a successful live birth as a result of IVF was less than 10%. In 2021, women younger than 35 years of age had a 43.1% probability of live birth from a single IVF attempt (Table 1)[38]; outcomes were worse with increasing age (31.0% for women 35 to 37 years of age, 19.0% for those 38 to 40 years of age, 9.4% for those 41 to 42 years of age, and 3.2% for those older than 42 years of age).

The process of an IVF cycle is shown in Figure 1. Exogenous gonadotropin stimulation is combined with suppression of the hypothalamic–pituitary axis with a gonadotropin-releasing hormone (GnRH) antagonist or, less frequently, an agonist to prevent an endogenous LH surge and override the body's natural system of avoiding multiple folliculogenesis. After stimulation for approximately 10 days, the final stages of oocyte maturation are initiated with human chorionic gonadotropin (HCG) or an GnRH agonist (or both), with the latter used to provide a shorter-acting burst of endogenous LH. Before oocytes are extruded, they are retrieved by means of needle aspiration guided by transvaginal ultrasonography and inseminated either by overlaying of concentrated sperm or by direct oocyte injection. Fertilized oocytes are grown in vitro for 5 days, by which time they have reached the blastocyst stage and are ready for uterine transfer. Embryo transfer can be performed at this time, but concern about supraphysiologic hormone exposure of the uterus has led to embryo transfers more commonly being performed after cryopreservation and thawing of the embryo. Cryopreservation and thawing allows the female partner time to recover from the oocyte retrieval

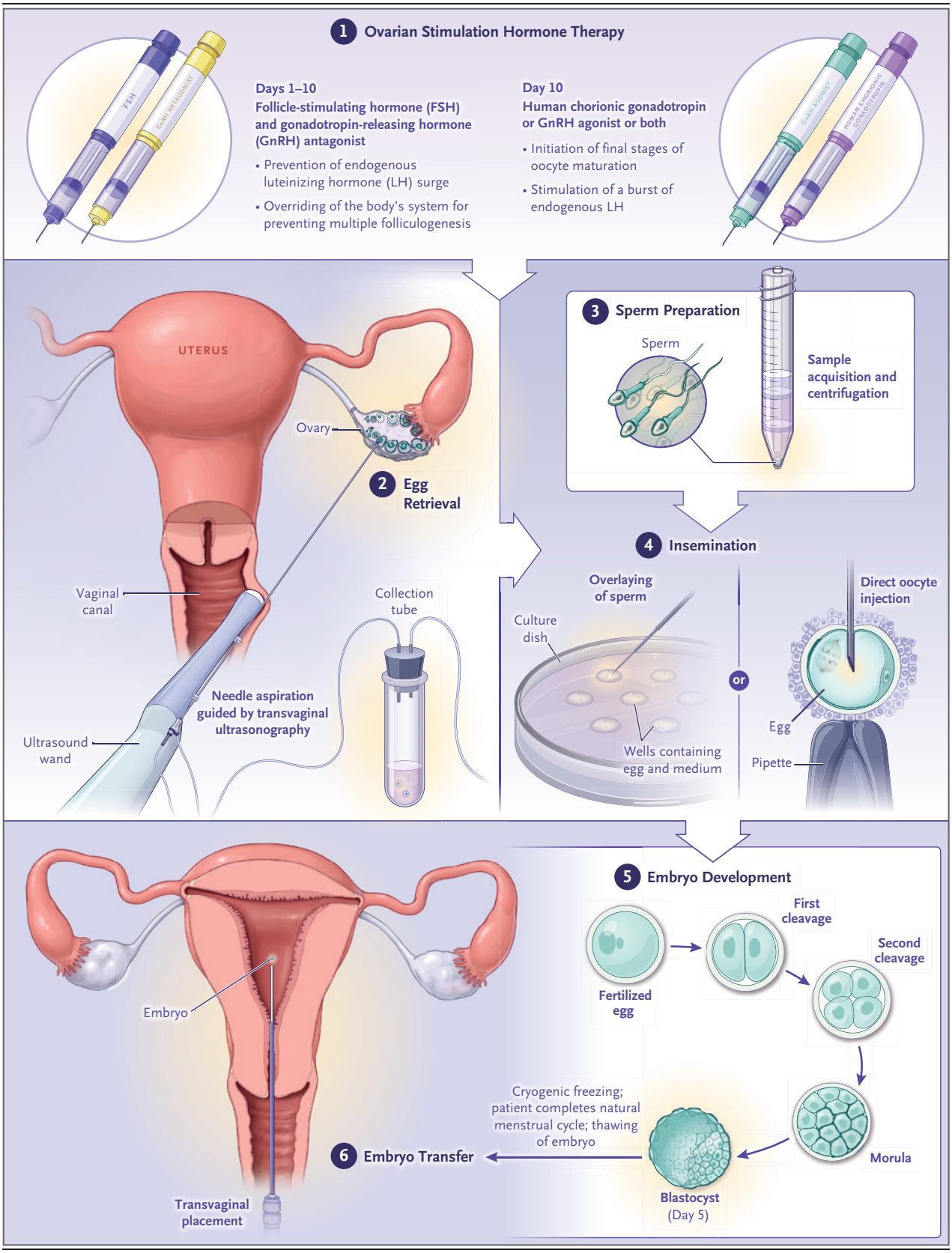

Figure 1 (facing page). Process of IVF.

procedure and to undergo either a natural menstrual cycle, wherein the embryo is implanted after ovulation occurs spontaneously, or a programmed cycle, in which the uterus is primed with exogenous estradiol and progesterone before embryo transfer.

Risks associated with IVF include ovarian hyperstimulation syndrome and multiple births. Ovarian hyperstimulation syndrome occurs with prolonged exposure to LH or HCG in susceptible persons when estradiol levels are extremely high. It can largely be avoided by adjusting the gonadotropin dose, cancelling and restarting the cycle at a lower dose if the response is too great, avoiding a "fresh" embryo transfer (rather than a transfer of the embryo after cryopreservation and thawing) if the estradiol level is too high, using lower doses of HCG to complete follicle maturation, and triggering final follicle maturation with a GnRH agonist to induce a burst of LH, which has a shorter half-life than HCG. Complications related to egg harvesting are rare (occurring in 1 in 1000 procedures) and include bleeding or trauma to the ovary or adjacent organs (or both) due to misplacement of the needle.

Multiple births resulting from IVF, an early concern with the technology, have decreased dramatically with the ability to grow embryos in vitro for 5 to 7 days. By this stage of development, embryo viability is so robust that transfer of a single embryo results in excellent live birth rates. In 2022, a total of 73.9% of all IVF cycles reported to the Society for Assisted Reproductive Technology involved the transfer of a single embryo, with an overall multiple pregnancy rate of 4% and almost no triplet pregnancies.[38]

GUIDELINES

Practice guidelines published by ASRM and the European Society for Human Reproduction and Embryology (ESHRE), among others, address the various types of infertility.[39] Some notable differences exist that may reflect regional policy considerations. For example, ASRM recommends routine initial testing for ovarian reserve,[40] but ESHRE does not recommend this approach in women with regular menses.[41] Our recommendations align with those of ASRM.

AREAS OF UNCERTAINTY

More evidence is needed with regard to the effects on fertility of endocrine-disrupting chemicals. The role of preimplantation genetic testing in IVF practice remains a subject of debate.[42] Although this testing may reduce the time to live birth, it risks the discarding of embryos that might otherwise be viable; because euploid cells develop more rapidly than aneuploid cells, embryos with aneuploid cell lines may outgrow the aneuploidy.[43]

The value of performing a fresh or natural cycle embryo transfer as compared with an artificial cycle in which exogenous estrogen is provided in physiologic amounts is of interest, because the risk of hypertensive disorders of pregnancy may be increased in the absence of a corpus luteum.[44] Finally, premature ovarian insufficiency and its precursor, decreased ovarian reserve, remain a barrier to pregnancy that is difficult to overcome with the use of current methods. The effects of supplying growth factors or stem cells to ovaries with limited remaining follicles are areas of active investigation.[45]

CONCLUSIONS AND RECOMMENDATIONS

Regarding the couple described in the vignette, the negative evaluation is diagnostic of unexplained infertility. Because they hope to have three children, we recommended IVF with storage of cryopreserved embryos for future use. Their IVF procedure resulted in 13 oocytes, 9 of which were fertilized and 6 of which became healthy blastocysts. One blastocyst was implanted during an IVF cycle, and a baby boy was born. We advised the couple to return 18 months after their son's birth to plan for implantation of one of the 5 remaining cryopreserved embryos. Their excellent yield of high-quality embryos makes it likely that this couple will achieve their desired family size.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril 2020;113:533-5.
2. Sunderam S, Kissin DM, Zhang Y, et al. Assisted reproductive technology surveillance — United States, 2018. MMWR Surveill Summ 2022;71:1-19.
3. Jackson-Bey T, Morris J, Jasper E, et al. Systematic review of racial and ethnic disparities in reproductive endocrinology and infertility: where do we stand today? F&S Reviews 2021;2:169-88 (https://www.fertstertreviews.org/article/S2666-5719(21)00011-6/abstract).
4. Rao PK, Boulet SL, Mehta A, et al. Trends in testosterone replacement therapy use from 2003 to 2013 among reproductive-age men in the United States. J Urol 2017;197:1121-6.
5. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update 2010;16:231-45.
6. Ford WC, North K, Taylor H, Farrow A, Hull MG, Golding J. Increasing paternal age is associated with delayed conception in a large population of fertile couples: evidence for declining fecundity in older men. Hum Reprod 2000;15:1703-8.
7. Scheffer JB, Scheffer BB, de Carvalho RF, Rodrigues J, Grynberg M, Mendez Lozano DH. Age as a predictor of embryo quality regardless of the quantitative ovarian response. Int J Fertil Steril 2017;11:40-6.
8. Tal R, Seifer DB. Ovarian reserve testing: a user's guide. Am J Obstet Gynecol 2017;217:129-40.
9. Seifer DB, Baker VL, Leader B. Age-specific serum anti-Müllerian hormone values for 17,120 women presenting to fertility centers within the United States. Fertil Steril 2011;95:747-50.
10. Devine K, Mumford SL, Wu M, DeCherney AH, Hill MJ, Propst A. Diminished ovarian reserve in the United States assisted reproductive technology population: diagnostic trends among 181,536 cycles from the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System. Fertil Steril 2015;104(3):612-619.e3.
11. Timur HT, Cimrin D, Gursoy Doruk O, Dogan OE. Determining the age group-based cut-off values of serum anti-Mullerian hormone concentrations to diagnose polycystic ovary syndrome. Curr Med Res Opin 2023;39:855-63.
12. Dewailly D, Lujan ME, Carmina E, et al. Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update 2014;20:334-52.
13. DeVilbiss EA, Sjaarda LA, Mumford SL. Routine assessment of ovulation is unlikely to be medically necessary among eumenorrheic women. Fertil Steril 2020;114:1187-8.
14. Chinta P, Rebekah G, T Kunjummen A, S Kamath M. Revisiting the role of serum progesterone as a test of ovulation in eumenorrheic subfertile women: a prospective diagnostic accuracy study. Fertil Steril 2020;114:1315-21.
15. Recent advances in medically assisted conception: report of a WHO Scientific Group. World Health Organ Tech Rep Ser 1992;820:1-111.
16. Christianson MS, Legro RS, Jin S, et al. Comparison of sonohysterography to hysterosalpingogram for tubal patency assessment in a multicenter fertility treatment trial among women with polycystic ovary syndrome. J Assist Reprod Genet 2018;35:2173-80.
17. Steiner AZ, Hansen KR, Barnhart KT, et al. The effect of antioxidants on male factor infertility: the Males, Antioxidants, and Infertility (MOXI) randomized clinical trial. Fertil Steril 2020;113(3):552-560.e3.
18. Boulet SL, Mehta A, Kissin DM, Warner L, Kawwass JF, Jamieson DJ. Trends in use of and reproductive outcomes associated with intracytoplasmic sperm injection. JAMA 2015;313:255-63.
19. World Health Organization. Polycystic ovary syndrome. February 7, 2025 (https://www.who.int/news-room/fact-sheets/detail/polycystic-ovary-syndrome#:~:text=The%20condition%20affects%20an%20estimated,particular%20related%20to%20metabolic%20problems).
20. Legro RS, Dodson WC, Kunselman AR, et al. Benefit of delayed fertility therapy with preconception weight loss over immediate therapy in obese women with PCOS. J Clin Endocrinol Metab 2016;101:2658-66.
21. Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med 2014;371:119-29.
22. Legro RS, Barnhart HX, Schlaff WD, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med 2007;356:551-66.
23. Tso LO, Costello MF, Albuquerque LET, Andriolo RB, Macedo CR. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev 2020;12(12):CD006105.
24. Gordon CM, Ackerman KE, Berga SL, et al. Functional hypothalamic amenorrhea: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2017;102:1413-39.
25. Meczekalski B, Katulski K, Czyzyk A, Podfigurna-Stopa A, Maciejewska-Jeske M. Functional hypothalamic amenorrhea and its influence on women's health. J Endocrinol Invest 2014;37:1049-56.
26. Luborsky JL, Meyer P, Sowers MF, Gold EB, Santoro N. Premature menopause in a multi-ethnic population study of the menopause transition. Hum Reprod 2003;18:199-206.
27. Yatavelli RKR, Bhusal K. Prolactinoma. In: StatPearls. Treasure Island, FL: StatPearls Publishing, 2023.
28. Ono M, Miki N, Amano K, et al. Individualized high-dose cabergoline therapy for hyperprolactinemic infertility in women with micro- and macroprolactinomas. J Clin Endocrinol Metab 2010;95:2672-9.
29. Strandell A, Lindhard A, Waldenström U, Thorburn J, Janson PO, Hamberger L. Hydrosalpinx and IVF outcome: a prospective, randomized multicentre trial in Scandinavia on salpingectomy prior to IVF. Hum Reprod 1999;14:2762-9.
30. Johnson N, van Voorst S, Sowter MC, Strandell A, Mol BW. Surgical treatment for tubal disease in women due to undergo in vitro fertilisation. Cochrane Database Syst Rev 2010;2010(1):CD002125.
31. Rikken JFW, Kowalik CR, Emanuel MH, et al. Septum resection versus expectant management in women with a septate uterus: an international multicentre open-label randomized controlled trial. Hum Reprod 2021;36:1260-7.
32. Practice Committee of the American Society for Reproductive Medicine. Removal of myomas in asymptomatic patients to improve fertility and/or reduce miscarriage rate: a guideline. Fertil Steril 2017;108:416-25.
33. Sallée C, Margueritte F, Marquet P, et al. Uterine factor infertility, a systematic review. J Clin Med 2022;11:4907.
34. Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. Obstet Gynecol Clin North Am 2012;39:535-49.
35. European Society of Human Reproduction and Embryology. ESHRE guideline endometriosis. February 2, 2022 (https://www.eshre.eu/Guideline/Endometriosis).
36. Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, gonadotropin, or clomiphene for unexplained infertility. N Engl J Med 2015;373:1230-40.
37. Reindollar RH, Regan MM, Neumann PJ, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril 2010;94:888-99.

38. Society for Assisted Reproductive Technology. Preliminary National Summary Report for 2022 (https://sartcorsonline.com/CSR/PublicSnapshotReport?ClinicPKID=&reportingYear=2022).
39. UpToDate. Society guideline links: female infertility. 2025 (https://www.uptodate.com/contents/society-guideline-links-female-infertility/print).
40. Practice Committee of the American Society for Reproductive Medicine. Fertility evaluation of infertile women: a committee opinion. Fertil Steril 2021;116:1255-65.
41. Romualdi D, Ata B, Bhattacharya S, et al. Evidence-based guideline: unexplained infertility. Hum Reprod 2023;38:1881-90.
42. Morales C. Current applications and controversies in preimplantation genetic testing for aneuploidies (PGT-A) in in vitro fertilization. Reprod Sci 2024;31:66-80.
43. Santoro N, Luu TH, Nel-Themaat L. Preimplantation genetic diagnosis in assisted reproductive technology. In: Reece EA, Leguizamon GF, Macones GA, Wiznitzer A, eds. Clinical obstetrics: the fetus and mother. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2021:169-78.
44. Epelboin S, Labrosse J, De Mouzon J, et al. Higher risk of pre-eclampsia and other vascular disorders with artificial cycle for frozen-thawed embryo transfer compared to ovulatory cycle or to fresh embryo transfer following *in vitro* fertilization. Front Endocrinol (Lausanne) 2023;14:1182148.
45. Herraiz S, Pellicer N, Romeu M, Pellicer A. Treatment potential of bone marrow-derived stem cells in women with diminished ovarian reserves and premature ovarian failure. Curr Opin Obstet Gynecol 2019;31:156-62.
46. Carson SA, Kallen AN. Diagnosis and management of infertility: a review. JAMA 2021;326:65-76.

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